

**Title:** A systematic review to study dose-response relationship of chimeric antigen T cell (CAR-T cell) therapy in adults with ALL, DLBCL and multiple myeloma

**Review question:** Is there a correlation between dose of CAR-T cell therapy and response in patients? Does the efficacy increase or decrease with increase in dose and vice versa? Does the incidence of AEs (CRS and neurotoxicity) increase or decrease with increase in dose and vice versa? What are the factors associated with response?

## PICO

**Patients:** Adults (age >18 years) with hematologic malignancies including ALL, DLBCL and MM

**Intervention:** CAR-T cell therapy

**Comparison:** Single arm and controlled studies

## Outcomes:

Efficacy outcomes: Overall response rate, progression free survival, overall survival, frequency of hematopoietic stem cell transplant after CAR-T therapy

Toxicity outcomes: Adverse events including cytokine release syndrome and neurological side effects.

**Databases:** Pubmed/medline

## Search terms:

1. "CAR" or "chimeric antigen receptor"
2. "CAR-T cell" and "acute lymphoblastic leukemia" or "ALL"
3. "CAR-T cell" and "diffuse large B-cell lymphoma" or "DLBCL"
4. "CAR-T cell" and "multiple myeloma" or CAR" or "MM"
5. "chimeric antigen receptor" and "acute lymphoblastic leukemia"
6. "chimeric antigen receptor" and "diffuse large B-cell lymphoma"
7. "chimeric antigen receptor" and "multiple myeloma"

## Eligibility criteria

### Inclusion criteria

1. All clinical studies (prospective and retrospective)

### Exclusion criteria

1. Articles reported in languages other than English
2. Conference presentations and abstracts (usually report interim data)
3. Studies in children
4. Studies in Solid tumors
5. Studies using Bispecific CAR-T cells
6. Studies using CAR-T cell cocktails (e.g. CD19 & CD20 targeting CAR-T cells)
7. Studies using Bispecific antibodies
8. Studies using Antibody drug conjugates

9. Articles reporting additional outcomes/post hoc analyses of previously published study
10. Preclinical studies
11. Systematic literature review articles
12. Review articles

**Search period**

Search period would include January 2010 and August 2021. One more search will be performed before finalizing the study results to include any recent studies

**Data extraction**

Screening of the papers based on title, abstract and full-texts will performed by two independent investigators. Discrepancies will be resolved through consensus discussion and when needed through third investigator. Studies meeting the eligibility criteria will be included in the review.

Following data will be extracted from the full-texts: study details (author name, year of publication, country, number of countries, number of centers and inclusion and exclusion criteria), patient characteristics (number of patients, cancer sub-type, lines of prior therapy, tumor burden), CAR-T cell details (dose and regimen, target antigen, co-stimulatory domains, gene transfer method, generation of CAR-T cells and persistence of CAR-T cells), efficacy outcomes (OS, PFS, ORR, Onset of response, DoR & markers of response) and safety outcomes (CRS and neurotoxicity, onset of CRS/neurotoxicity)

**Risk of bias (quality) assessment**

Study quality and risk of bias will assess using the ROBINS-I tool. Characteristics of the study including selection criteria, confounding factors, study deviations and handling of missing data will be assessed. Based on the assessments, each study will be categorized as low risk, moderate risk, serious risk and critical risk of bias. Assessment will be performed by two independent investigators and discrepancies will resolved through consensus or when needed through third investigator.

**Data analysis**

We do not plan to perform meta-analysis of population data.